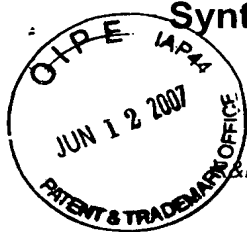


Appendix:

The Appendix includes the following item:

- article entitled "Synthesis and Properties of Degradable Poly(urethane area)s To Be Used for Ligament Reconstructions" by Karin GISSELFALT et al.



Synthesis and Properties of Degradable Poly(urethane urea)s To Be Used for Ligament Reconstructions

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In the present study we describe the synthesis, wet spinning, mechanical testing, and degradation of poly(urethane urea)s (PUURs) intended for clinical use in anterior cruciate ligament (ACL) reconstruction. The effects of soft segment chemical composition and molar mass and the kind of diamine chain extender on the material properties were investigated. It was found that the fibers made of PUUR with polycaprolactone diol (PCL530) as soft segment and MDI/1,3-DAP as hard segment (PCL530-3) have high tensile strength and high modulus and when degraded keep their tensile strength for the time demanded for the application. In conclusion, from a chemical and mechanical point of view PUUR fibers of PCL530-3, ARTELON, are suitable for designing a degradable ACL device.

Introduction

Ligament injuries in the knee joint are among the most common sporting injuries.^{1,2} Ruptures of the anterior cruciate ligament (ACL), the primary and most important stabilizer of the knee³ are the most common serious ligament injuries. In the 1960s the first ACL reconstructions with synthetic materials were performed.⁴ The introduction of ligament prostheses generated much interest because it offered the benefit of quick recovery and rapid rehabilitation.⁵ While early results were promising, the long-term results were disappointing. A number of problems were reported, including irreversible elongation, rupture, and formation of wear debris.

Materials used for these prosthetic devices or reinforcement ligament bands were, e.g., poly(tetrafluoroethylene) poly(ethylene terephthalate)^{1,4,6–9} polypropylene, polyethylene, carbon fibers¹⁰ and polydioxanone.¹¹ The common properties of these materials are a too high elastic modulus compared to native ACL and permanent deformation after repeated loading due to nonelastic behavior.

Materials with elastic behavior and modulus above rubber level can be found among the multiblock copolymers. Poly(urethane urea)s (PUUR) are multiblock copolymers, which combine excellent mechanical properties with documented blood compatibility.^{12,13} These properties have favored the use and development of PUUR as biomaterials, particularly as products for blood applications.^{14–17}

PUURs are made of soft segments based on polyether or polyester and hard segments based on the reaction of diisocyanate and diamine chain extender. Due to the thermodynamic incompatibility between the two segments PUURs undergo microphase separation resulting in the phase-separated heterogeneous structure that can be consid-

ered as hard segment domains dispersed in a soft segment matrix. The various physical properties of the material such as strength, modulus, and elasticity are closely correlated with the domain structure and the interaction between the segments inside the domain. By adjusting the chemical nature and respective amounts of reagents, it is possible to obtain a wide range of materials with different properties. Thus materials may be tailored for various applications.

In the design of a degradable device for ACL reconstruction, whether a true prosthesis or an augmentation device many biological and mechanical criteria must be met. High initial strength is needed to prevent mechanical failure of the implant prior to tissue ingrowth.¹⁸ In addition, a moderate degradation rate is required to induce ingrowth of organized tissue.¹⁹ If degradation is too rapid, the host tissue may be exposed to stresses that are too great, resulting in failure. On the other hand, if the degradation is too slow, stress shielding may occur.¹⁹ Thus, a new material for ACL reconstruction should be (1) compatible with surrounding tissues and allow cell ingrowth, (2) intended to be mechanically similar to native ACL, (3) degradable, but keeping at least 50% of its strength and stiffness for at least 9–12 months. A possible way to fulfill these requirements is to use a textile composition made of degradable PUUR fibers. Thus, the aim was to make PUUR fibers suitable for designing a degradable ACL device. Previously made PUUR fibers of the Spandex type, e.g., Lycra, are unsatisfactory for use as ligaments. In particular, their elastic modulus is too low and they are not degradable.

In this paper the synthesis, wet spinning, mechanical properties, and degradation of a number of PUUR fibers are presented. The effects of soft segment chemical composition and content and the kind of diamine chain extender on the material properties are investigated.

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Table 1. Composition and Solubility of PUURs

sample code	chain extender	soft segment \bar{M}_n	hard block content (%)	DMF solution (18%, 22 °C)	$M_{peak} \times 10^{-3}^c$
PDEA2000-2	EDA	2000	23.0	opaque ^a	86
PDEA1000-2	EDA	1000	37.7	opaque	86
PDEA500-2	EDA	500	55.9	opaque	115
PCL2000-2	EDA	2000	23.0	opaque	105
PCL1250-2	EDA	1250	33.0	opaque	121
PCL530-2	EDA	530	51.4	opaque	125
PCL530-2Me	1,2-DAP	530	52.0	clear ^b	106
PCL530-3	1,3-DAP	530	52.0	clear	125
PCL530-4	1,4-DAB	530	53.0	opaque	123
PCL530-5	1,5-DAPe	530	53.6	opaque	106
PCL530-6	1,6-DAH	530	54.2	opaque	106

^a Opaque: hazy, poorly solubilized in the above condition. ^b Clear: transparent, absolutely solubilized in the above condition. ^c Poly(ethylene oxide) equivalent M_{peak} .

Experimental Section

Materials Polycaprolactone diols (PCL) ($\bar{M}_n = 530$ g/mol) and ($\bar{M}_n = 1250, 2000$ g/mol) were obtained from Solvay and Aldrich, respectively. Adipic acid, di(ethylene glycol), di-*n*-butylamine, ethylenediamine (EDA), 1,2-diaminopropane (1,2-DAP), 1,3-diaminopropane (1,3-DAP), 1,4-diaminobutane (1,4-DAB), 1,5-diaminopentane (1,5-DAPe), 1,6-diaminohexane (1,6-DAH), and lithium chloride (LiCl) were purchased from Fluka. 4,4'-Diphenylmethane diisocyanate (MDI) was provided by Bayer AB. *N,N*-Dimethylformamide (DMF) 99.8% and toluene 99.8% were obtained from Labscan.

Polyester Synthesis Hydroxytelechelic polyesters were synthesized from adipic acid and di(ethylene glycol) with acid catalyst until the acid number was <2 as determined by titration of aliquots with 0.1 M KOH in ethanol. The removal of water to drive the reaction at a reasonable rate was achieved by azeotropic distillation with toluene. Three products with hydroxyl numbers of 56 ($\bar{M}_n = 2000$ g/mol), 112 ($\bar{M}_n = 1000$ g/mol), and 223 ($\bar{M}_n = 500$ g/mol) respectively, as determined according to ASTM D 4274-94 were used in the present study.

Polymerization PUURs²⁰ were synthesized by a two-step method described earlier.²¹ In the first step a prepolymer was formed. The polyester diol was added slowly to 4,4'-diphenylmethane diisocyanate (MDI) (NCO:OH = 2.05:1) in bulk at 50 °C in a dry N₂ atmosphere. The isocyanate content was determined by reacting the prepolymer with an excess of di-*n*-butylamine in toluene. After the reaction was complete, the excess di-*n*-butylamine was determined by back-titration with standard hydrochloric acid.

In the second step a dilute solution of diamine chain extender and monoamine chain stopper in DMF was added rapidly to a solution of prepolymer in DMF (20 wt %) under intense stirring at 20 °C. The molar ratio NCO:NH₂ was 1:1 with 2% monoamine. The final polymer content was 18 wt %. The chemical compositions of the various PUURs can be seen in Table 1.

Fiber Spinning Fibers were prepared by a wet spinning process²¹ (equipment from Bradford University Research Limited, Bradford, England). The polymer solution was metered through a spinneret (120 holes, 80 μ m diameter) submersed in a coagulating bath containing water. In a

second water bath the fiber bundle was drawn after which the multifilament fiber was taken up on a spool. The temperature in the water baths was varied from 20 to 80 °C to get as high a draw ratio as possible. The spools with fibers were rinsed in running tap water overnight and dried at room temperature. For each batch of fibers linear density, tensile strength, stiffness, and elongation at break were determined.

Band Production The wet spun multifilament fibers were by doubling and slight twisting converted to a coarse yarn which was used as warp threads. The bands were woven on a narrow fabric needle loom (type FX2/65, Mageba Textilmaschinen Vertriebs GMBH, Germany) with low weft tension in plain weave to utilize as much as possible of the yarn strength combined with good stability.

Density Measurements The density of the fibers was measured with a Micromeritics Multivolume Pycnometer 1305.

Porosity Measurements Pore sizes and pore size distributions of the woven bands were measured by mercury porosimetry, Micromeritics AutoPore III 9410.

Polymer Degradation Samples of fibers and bands were placed in vials in a great surplus of 0.06 M phosphate buffer solution pH 7.4 (Na₂HPO₄ and KH₂PO₄).²² The sealed vials were placed in thermostat ovens at 37 and 77 °C. At intervals the vials were opened and aliquots of material were taken out. Changes in molar mass and loss of tensile strength were investigated.

Size Exclusion Chromatography (SEC) SEC was conducted with a Waters 2690 Separations Module equipped with a Waters 996 photodiode array detector and a Waters 2410 refractive index detector. Two Styragel columns, HT6E and HT3, were operated in series at a flow rate of 1 mL/min in DMF containing 0.5% (w/v) LiCl to prevent aggregation. The retention times were converted to apparent molar masses using poly(ethylene oxide) standards.

Linear Density Measurements The linear density of the fibers was determined by weighing of a known length of fiber, typical 100 m, and is presented in tex. The tex unit is defined as g/1000 m.

Mechanical Testing After equilibration with water at 20 °C for 30 min, the multifilament fibers and the woven bands were tested in the wet state in a tensile tester (UT 350/5 LS universal testing machine, SDL International Ltd. Stockport).

The constant rate of extension was 900 mm/min, and the sample lengths were 100 mm for fibers and 30 mm for the woven bands

Differential Scanning Calorimetry (DSC) Thermal analysis was carried out on a Perkin-Elmer Pyris1. The heating rate was 10 °C/min over a temperature range of -100 to 150 °C. The sample was cooled to -100 °C, and then a second run was performed. Glass-transition temperatures were determined from the second scan

Results and Discussion

Polymerization In a first study, PUURs were synthesized using poly(di(ethylene glycol) adipate) (PDEA) or polycaprolactone diol (PCL), with different molar masses as soft segments, MDI and EDA as chain extender (Table 1). The length of the soft segment was altered by changing the molar mass of the polyesterdiol while the length of the hard block was unchanged. However, there was a distribution of hard block lengths as a consequence of the stoichiometric ratio in the prepolymerization step²³ As the soft segment was shortened from 2000 to 500 g/mol the hard block content increased from 23% by weight to 55%. An immediate effect was that the solubility in DMF decreased with increasing hard block content, resulting in turbidity and gelation a few minutes after chain extension

Another series of PUURs was prepared using PCL530 as soft segment, MDI, and six different aliphatic diamines as chain extenders (Table 1)

The different chain extender structures affected the solubility of the polymer in DMF. These PUURs have almost the same hard/soft ratio and showed solubility in the order 1,2-DAP > 1,3-DAP > 1,5-DAPe > 1,6-DAH > 1,4-DAB > EDA. In the reactions all diamines but 1,2- and 1,3-DAP gave rise to turbid solutions 5–20 min after chain extension. After still some time brittle gels were formed. 1,3-DAP formed clear polymer solutions, but they were turbid and gelled after a few days. PCL530-2Me solutions remained clear for at least 1 year. This is the most apparent difference between 1,2-DAP and the other five chain extenders and is explained in terms of less efficient hydrogen bonding due to steric effects from the pendant methyl group. Similar behavior has been seen for PUUR systems chain extended with aromatic diamines with substituents that increased the steric effects²⁴

The lower solubilities of the other PUURs probably depend on the influence of the urea structure on the association behavior. PUUR solutions with even number of methylene groups in the chain extender got turbid very soon while chain extenders with odd-numbered methylene groups remained clear for longer times. Similar results were found by Joel et al.²⁵ who studied steric odd–even effects of various urea structures of PUUR on solution properties in DMF. They found that the viscosity of solutions with odd numbers of methylene groups was independent of time, while the even-numbered ones showed turbidity and a drastic increase in viscosity with time followed by gelation. The turbidity was explained by formation of a higher concentration of physical cross-links caused by hydrogen bonding within the hard

block domains²⁶ The solution process becomes restricted if the hard segment domains are perfectly arranged and form a physically cross-linked network. Thus, the good solubility of PCL530-3 may be explained by a lower degree of hydrogen bonding compared to the other chain extenders

A requirement for spinnability is that the polymer is soluble. The solvent, DMF, should prevent gelation due to hard segment interaction before spinning, but the solubility of PUUR in DMF is poor. By adding LiCl (0.07 g of LiCl/g of polymer solution) to the polymer solutions turbidity could be removed and gelation could be prevented²⁵ The increased solubility is based on the destruction of the hydrogen bonds between chains and on a simultaneous blocking of the acceptor positions owing to the favored complex formation between Li and carbonyl oxygen²⁷

Fiber Spinning The fibers are formed in a wet spinning process. In the first step precipitation occurs and the solvent diffuses out of the extrudate into the bath, and nonsolvent diffuses from the bath into the extrudate. The rate of the coagulation has a profound effect on the yarn properties. Important process variables are, for example, concentration and temperature of the spinning solution, composition, and temperature of the coagulation bath

The temperature of the spinning solutions was kept within 20–25 °C and the polymer concentration was 18 wt %. No correlation between polymer content and tensile properties could be seen. However, a spinning solution viscosity of more than 1 Pa s was needed to be able to get a stable spinning process

The temperature of the coagulation bath was found to be of great importance. The rate of PUUR coagulation occurring when the polymer solution was extruded into the water depends on the coagulation temperature and influences both the morphology of the undrawn fiber and the ultimate fiber properties. The suitable spin bath temperature for PDEA-based PUURs was about 20 °C (Table 2). At higher temperatures the polymer got stuck in the spinneret. In contrast the PCL-based PUURs seemed to be easier to spin the higher the temperature (Table 2). This difference between the two polyesters can be due to their difference in hydrophilicity²⁸

In the second water bath the fiber bundle is drawn to get molecular chain orientation and thereby improve the mechanical properties. The higher the draw ratio, the lower the elongation and the stiffer and stronger the fiber

The effect of draw ratio on tensile properties for PCL530-3 is seen in Figure 1

The draw ratio of the fibers is dependent on the temperature not only in the coagulation bath but also in the stretching bath. It was found that the best processability and draw ratio were achieved when the baths had the same temperature. The spinning conditions are shown in Table 2. Three different groups are identified. The first group contains PDEA-based PUURs, described earlier, which have the best processability and draw ratio at 20 °C. The second group contains PCL-based PUUR chains extended with EDA spun from DMF + LiCl and PCL530-2 Me and PCL 530-3 spun from DMF. These obtain their highest draw ratio at 60 °C and their drawability is directly proportional to the temper-

Table 2. Spin Parameters for Different PUURs

sample code	spin solvent	$T_{\text{draw optimal}}^a$ (°C)	draw ratio _{20°C} / draw ratio _{$T_{\text{draw optimal}}$}	draw ratio
PDEA2000-2	DMF + LiCl	20		5
PDEA1000-2	DMF + LiCl	20		5
PDEA500-2	DMF + LiCl	20		4.5
PCL2000-2	DMF + LiCl	60	0.58	6
PCL1250-2	DMF + LiCl	60	0.57	6
PCL530-2	DMF + LiCl	60	0.72	5
PCL530-2Me	DMF	60	0.67	9
PCL530-3	DMF	60	0.72	5.4
PCL530-3	DMF + LiCl	80	0.44	5.4
PCL530-4	DMF + LiCl	80	0.70	5.4
PCL530-5	DMF + LiCl	80	0.46	6.4
PCL530-6	DMF + LiCl	80	0.54	7.4

^a $T_{\text{draw-optimal}}$ = the temperature at which the highest draw ratio is achieved.

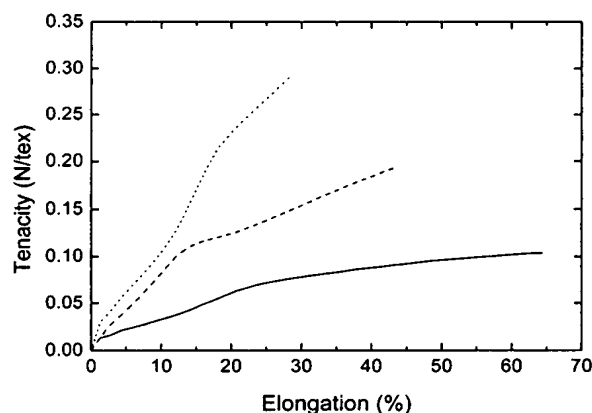


Figure 1. Tensile test diagrams for PUUR fiber of PCL530-3 showing changes produced by increasing orientation and improving structure. Draw ratios were (—) 3.5, (---) 3.8, and (···) 5.4.

ature. In the third group the highest draw ratio is achieved at 80 °C, maybe it is possible to increase their draw ratio further if the temperature is raised further. This group contains PCL-based PUUR with chain extenders with more than two methylene groups and are spun from DMF + LiCl. Even though the highest draw ratio was achieved at the same temperature within each group, the temperature dependence of draw ratio of the fibers differed (Table 2 and Figure 2)

The increase in draw ratio of PCL530-5 was almost proportional to the temperature, while the increase in draw ratio of PCL530-3 showed weak temperature dependence between 20 and 50 °C. Above that interval the drawability was directly proportional to the temperature. The drawability of PCL530-4 and PCL530-6 was constant at temperatures below 60 and 70 °C, respectively. At these temperatures strong temperature dependence in drawability appeared. Additional investigations are needed to explain these differences.

Band Production The appropriate force at break of the finished and sterilized band should be 1200 N. On the basis of practical experiences the theoretical breaking force therefore was chosen to 1600 N in order to calculate the resulting cross section of the band as well as the number of fibers needed. Furthermore the diameter of the band was not allowed to exceed 5 ± 1 mm. In the finished band three circular yarns are placed in a triangular form. Assuming

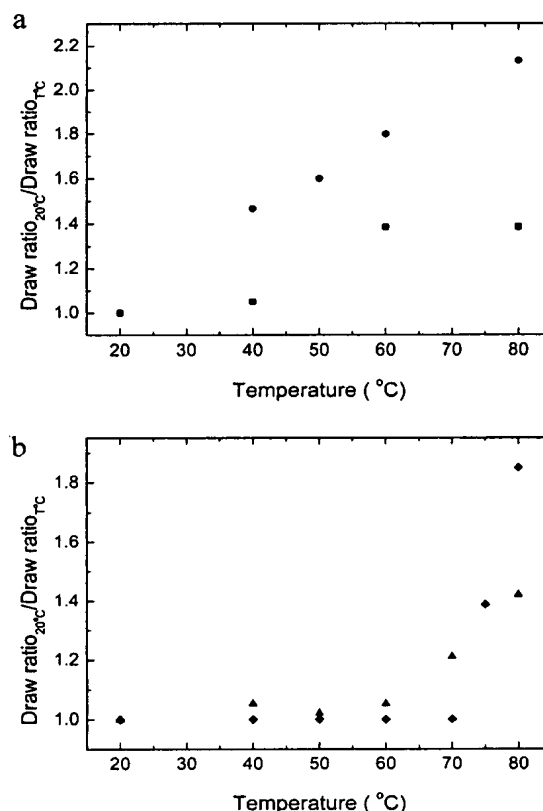


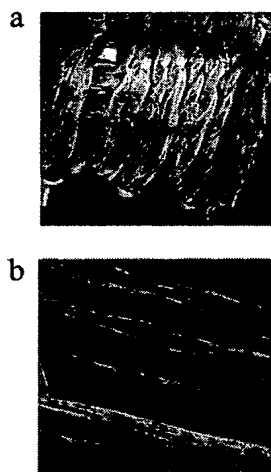
Figure 2. Draw ratio_{20°C}/draw ratio _{T_c} : (a) (■) PCL530-3 and (●) PCL530-5; (b) (▲) PCL530-4 and (◆) PCL530-6.

hexagonal close packing of the fibers in the yarn²⁹ the yarn radius can be calculated. From the calculations it is given that the tenacity of the fibers should be at least 0.2 N/tex to meet the criteria of strength and size.

Porosity Measurements In medical applications the pore sizes and their distributions are of great importance for promoting cell ingrowth. The multifilament fibers made from wet spinning have a high void content. Furthermore, when fibers are processed into woven structures, varying degrees of porosity can be provided. The pore sizes and pore size distribution of two woven bands made of 1500 multifilament PCL530-3 fibers are presented in Table 3. The smallest pores <8 μm , are probably between the filaments in the multifilament fiber while pores between 8 and 600 μm are the spaces

Table 3. Pore Sizes and Pore Size Distributions of PUUR Bands

interval (μm)	pores (%)	interval (μm)	pores (%)
401–600	6.8	21–50	28.3
201–400	15.6	8–20	10.7
101–200	8.0	1.0–7.9	4.5
51–100	20.7	<1	5.4

**Figure 3.** SEM micrographs of the surface of (a) wet spun and woven PUUR fiber bar = 50 μm and (b) wet spun PUUR fiber bar = 5 μm .

between the fibers in the warp and weft (Figure 3). Almost half of the pores (49%) are 21–100 μm , sizes that may be suitable for fibrous connective tissue ingrowth.³⁰ About 20% of the pores are 100–400 μm , pore sizes which have been shown to be suitable for osteoblast ingrowth in hard tissue applications.³¹

Mechanical Testing The tensile properties of the fibers are shown in Table 4. In the first series the length and composition of the esterdiol were varied and the hard block was formed from MDI and EDA. The effects upon shortening the soft segment were seen in increased stiffness and decreased elongation of the fibers. The largest effect is seen when comparing polymers made from soft segments of molar masses of ~ 1000 and ~ 500 g/mol. As a consequence of the shortening of the soft segment the hard/soft ratio increases. The hard blocks, which are extensively hydrogen bonded mainly affect the stiffness and serve as both cross-links and filler particles in the soft segment matrix. It is known that the strength and modulus of polyurethane copolymers are directly related to the amount and stability of the hard segment domains.³² Wang and Cooper³² studied the effect of the hard block content and block length on the morphology and properties of PUURs systematically. They found that the mechanical properties depended primarily on the hard block content and the strong hard-domain cohesion due to interurea hydrogen bonding that resulted in semicrystalline behavior.

The effects on the mechanical properties of the PCL530-based PUUR fiber chains extended with six different aliphatic diamines were investigated (Table 4). The hard segment content is almost constant, but their structures differ. The strongest fibers were obtained from PCL530-2Me and PCL530-3, which are supposed to be less efficiently hydrogen bonded in solution compared to the other PUURs

PCL530-2Me and PCL530-3 formed clear solutions and could be spun without addition of LiCl. As LiCl was added to a PCL530-3 solution the tenacity of the fiber produced thereof decreased more than 40%. Nevertheless, the tenacity of PCL530-3 fiber from DMF + LiCl was still among the highest. Upon a comparison of fibers spun from DMF–LiCl solutions PCL530-3 and PCL530-5 are the strongest. Thus chain extenders with an odd number of methylene groups tend to form stronger fibers than those with even numbers. From the design of the ACL reconstruction band, it was given that the fiber should have a tenacity of at least 0.2 N/tex. Only two of the tested fibers, made from PCL530-3 and PCL530-2Me, met this requirement.

Bands A typical tensile test diagram of a band of PCL530-3 fibers is given in Figure 4. The shape of the load-elongation curve of the band is similar to that of the fiber but the elongation is higher. This is expected as the fibers are slightly twisted to get a coarse yarn before weaving.

Differential Scanning Calorimetry The glass transition temperatures of the soft blocks for the different PUURs are presented in Table 5. As the molar mass of the soft segments decreased, the T_g increased from -30.7 to -5.5 $^{\circ}\text{C}$ and from -48.3 to -11.3 $^{\circ}\text{C}$ for PDEA and PCL, respectively. The T_g was harder to detect the shorter the soft segment. The effect of soft segment length on its T_g is related to the limitation of the soft segment mobility imposed by the attached hard segment. Beside the molar mass of the soft segment, the chain extender affected the T_g to some extent. PCL530-2Me and PCL530-3 showed the highest T_g . For chain extenders with three or more methylene groups, there was a movement toward higher T_g the longer the diamine. All PUUR fibers but PCL530-2Me and PCL530-3 were spun from DMF + LiCl. PCL530-3 spun from DMF + LiCl showed no change in T_g compared to PCL530-3 spun from DMF. The phase mixing of soft and hard segments makes thermal molecular motion in soft segment phase restricted. Therefore, the shifts of T_g to higher temperatures are attributed to the interaction between hard and soft segments.

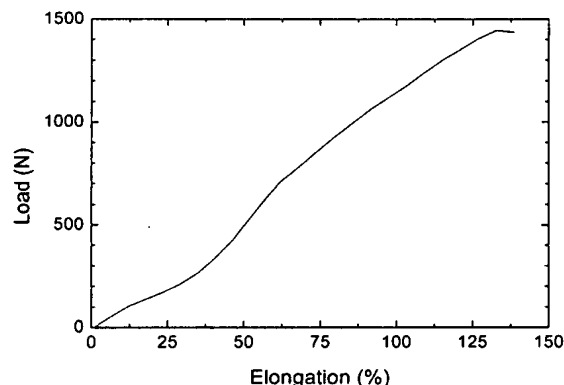
Degradation Studies Among the various bonds present in PUUR, the most susceptible ones are the ester bonds of the soft segments which upon hydrolysis yield carboxylate and hydroxyl groups. The acid produced can catalyze the ester hydrolysis so that an autocatalytic reaction becomes prevalent. Furthermore, the intended use for the material is in the knee that has a neutral pH.³³ For that reason all degradation studies were carried out in a great surplus of buffered solutions at pH 7.4. Both changes in molar mass and tensile strength of optimal drawn fibers and bands thereof were studied. The data for fibers and bands obey the same dependence on change in molar mass and tensile strength. Thus, the differences in fiber packing and sample thickness do not seem to have any effect on degradation rate.

The loss in tensile strength with hydrolysis time at 77 $^{\circ}\text{C}$ is shown in Figure 5.

For both PDEA- and PCL-based PUUR the polymer with longer soft segments degraded faster. Thus, PDEA2000 and PCL2000 display lower hydrolytically stability than PCL530 and PDEA500, respectively. The reason is a higher fraction

Table 4. Mechanical Properties of Different PUUR Fibers

sample code	spin solvent	tenacity (N/tex) ^a	stiffness $\times 10^3$ (N/mm)	elongation at break (%)
PDEA2000-2	DMF	0.06 \pm 0.004	6 \pm 0.5	130 \pm 13
PDEA1000-2	DMF	0.06 \pm 0.004	6 \pm 0.4	120 \pm 10
PDEA500-2	DMF + LiCl	0.08 \pm 0.005	17 \pm 1	50 \pm 5
PCL2000-2	DMF + LiCl	0.13 \pm 0.007	6 \pm 0.3	77 \pm 12
PCL1250-2	DMF + LiCl	0.11 \pm 0.005	6 \pm 0.4	74 \pm 14
PCL530-2	DMF + LiCl	0.10 \pm 0.01	45 \pm 2	32 \pm 8
PCL530-2Me	DMF	0.25 \pm 0.015	50 \pm 3	29 \pm 4
PCL530-3	DMF	0.28 \pm 0.01	62 \pm 4	40 \pm 3
PCL530-3	DMF + LiCl	0.16 \pm 0.008	50 \pm 3	34 \pm 2
PCL530-4	DMF + LiCl	0.10 \pm 0.01	60 \pm 3	25 \pm 3
PCL530-5	DMF + LiCl	0.16 \pm 0.015	56 \pm 3	28 \pm 10
PCL530-6	DMF + LiCl	0.11 \pm 0.01	70 \pm 3	16 \pm 5

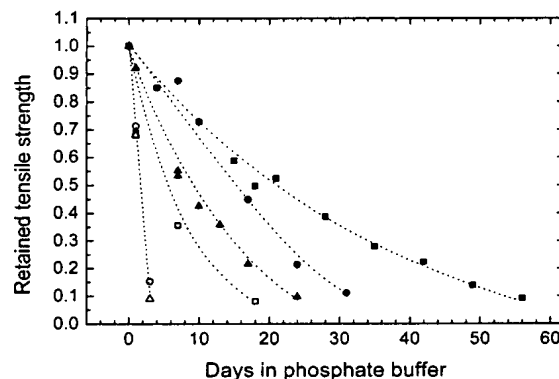
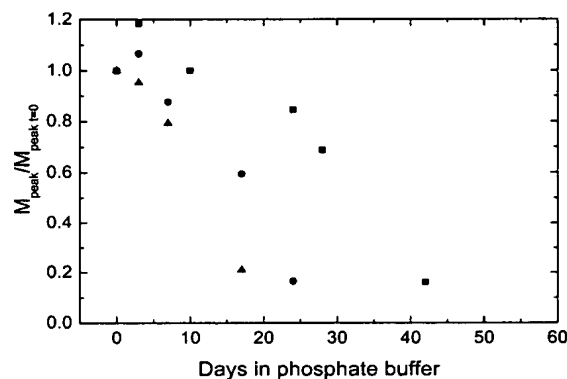
^a Density of fibers = 1.23 g/cm³.**Figure 4.** Typical tensile test diagrams for a PUUR band of PCL530-3 fibers.**Table 5.** DSC Data

sample code	soft segment T_g (°C)	sample code	soft segment T_g (°C)
PDEA2000-2	-30.7	PCL530-2Me	-9.2
PDEA1000-2	-25.7	PCL530-3	-8.4
PDEA500-2	-5.5	PCL530-3 (LiCl)	-8.3
PCL2000-2	-48.2	PCL530-4	-10.2
PCL1250-2	-39.1	PCL530-5	-11.2
PCL530-2	-11.3	PCL530-6	-13.7

of soft segments and, consequently, of ester groups exposed to hydrolysis

The chemical composition of the ester affects the degradation rate of the different PUURs. PUURs with soft segments made of PDEA degrade faster than those based on PCL. The superior resistance to hydrolysis is ascribed to the hydrophobicity of PCL. It has been shown that the introduction of hydrophilic poly(oxyethylene) blocks in PCL-POE-PCL triblock copolymers did increase the hydrophilicity and degradation rate compared with the homopolymer PCL.²⁸ PDEA500 contains about three diethylene glycols whereas the PCL diols initiated with diethylene glycol contain one

The initial molar mass of the different PUURs varied to a small extent (Table 1). The rate of the decrease in tensile strength was not affected, but the time to complete degradation became somewhat shorter the lower the initial molar mass. The molar mass decreases after an induction period of about 10 days for PCL530-2 and -3 and about 3 days for PCL1250-2 (Figure 6). No induction period was seen for

**Figure 5.** Tensile strength retention as a function of hydrolysis time of different PUURs at 77 °C: (■) PCL530-2 and PCL530-3; (●) PCL1250-2; (▲) PCL2000-2; (□) PDEA500-2; (○) PDEA1000-2; (△) PDEA2000-2.**Figure 6.** Molar mass as a function of hydrolysis time of different PCL-based PUURs at 77 °C: (■) PCL530-3; (●) PCL1250-2; (▲) PCL2000-2.

the other samples. During the induction period a decrease in SEC retention time was seen. The phenomenon has been occasionally reported by some researchers using both in vitro and in vivo systems³⁴⁻³⁶ but no unanimous conclusions on the reasons for the increase were drawn. We have interpreted the decrease in retention time, as aggregation of the polymer due to a physical process, since no unreacted isocyanate groups is present in the polymers. Furthermore, despite the increase in molecular size, the tensile strength decreased already after 2 days in phosphate buffer (Figure 5)

One of the requirements of the material was that at least 50% of the tensile strength should be kept for at least 9–12

months. For use at body temperature it is interesting to estimate and investigate the conformity between the degradation rate at 37 and 77 °C

Since fibers of PCL530-3 seem to have the most promising properties from many aspects, further degradation studies of these fibers at 37 °C were made. The change in molar mass at 37 °C follows the same pattern as that at 77 °C. After about 40 days a decrease in SEC retention time for the polymer is seen, which is similar to the results after 2–3 days at 77 °C. After that the retention time is constant for a long period of time. This means that the size of the formed aggregates is to some extent independent of the molar mass of the molecules that takes part in the aggregate formation. It is obvious that the degradation proceeds since after 500 days the SEC retention time has increased accompanied by a loss in tensile strength of 5–10%. Thus, the degradation rate at 37 °C seems to be about 1/20th lower than that of the degradation rate at 77 °C

In addition to loss of tensile strength and molar mass, the mass change of the PCL530-3 fibers has been studied. First the mass of the fibers increased about 8–10% due to water adsorption. After 52 days at 77 °C, there were signs of mass loss and after another 10 days the mass loss is obvious (–30%). At that time the fibers were very brittle, and further measurements were hard to perform. In accordance with the low degradation rate at 37 °C, it is not expected to see any decrease in the mass before 800–850 days of degradation

Regarding the biocompatibility of the PCL530-3, both safety studies, mutagenicity and delayed contact hypersensitivity, and implantation studies have been performed and reported.³⁷ When PUUR bands made of PCL530-3 fibers were used as ACL prosthesis in rabbits and minipigs, bone formation was seen in the drilled tunnels and surrounding the PUUR fibers. Also, irrespective of observation time connective tissue ingrowth was observed between and in close contact with the PUUR fibers in both species. At observation times exceeding 6 months, the connective tissue had an orientation of the collagen fibers and fibroblasts in parallel with the PUUR fibers.³⁷ From clinical trials using the PUUR band as an ACL augmentation, biopsies were obtained from 5 patients at times between 30 and 40 months. As in the animals a high percentage of connective tissue ingrowth was found in close contact with the material and the presence of collagen type I and blood vessels was confirmed using immunohistochemical methods. No indications of obvious inflammatory reaction or foreign body response were detected

Conclusions

We have demonstrated that the chemical composition of PUUR can be tailored to get fibers with strength, stiffness and degradation rate, which fulfill the desired properties of a material for ACL reconstruction

Fibers made of PUUR based on PCL530 have superior strength and stiffness compared to other polyesterdiols used in the study and keep at least 50% of its original tensile strength more than 9 months at body temperature. Further-

more, chain extension of PCL530:MDI with 1,3-DAP produces a polymer solution from which strong fibers can be spun without additives. A porous band with appropriate strength and size can be woven with the fibers

In conclusion, from chemical and mechanical points of view, fibers of PCL530-3, ARTELON, are suitable for designing a degradable ACL device. Human clinical trials with ACL reconstruction using the PUUR band are in progress

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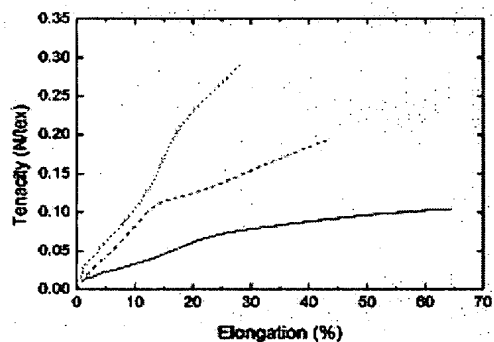


Figure 1. Tensile test diagrams for PUUR fiber of PCL530-3 showing changes produced by increasing orientation and improving structure. Draw ratios were (—) 3.5, (---) 3.8, and (···) 5.4.

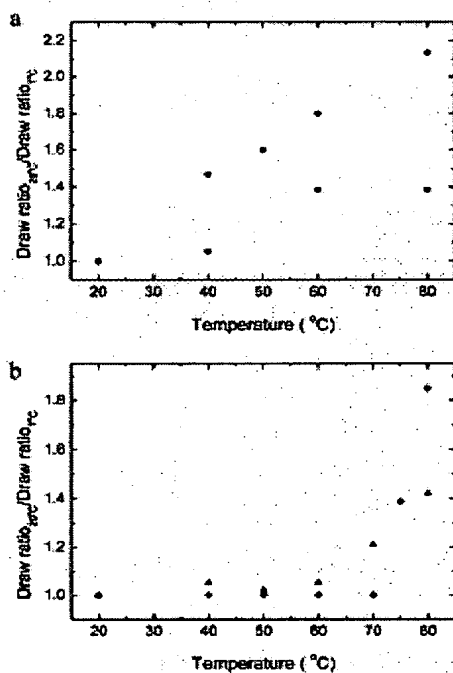


Figure 2. Draw ratio_{sp}/draw ratio_{rc}: (a) (■) PCL530-3 and (●) PCL530-5; (b) (▲) PCL530-4 and (♦) PCL530-6.

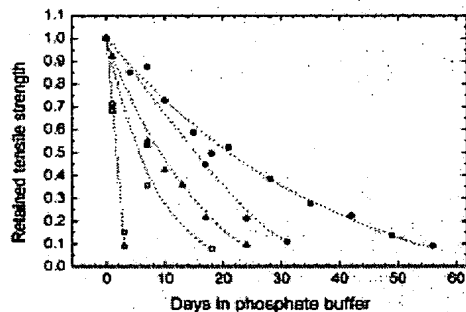


Figure 5. Tensile strength retention as a function of hydrolysis time of different PUURs at 77 °C: (■) PCL530-2 and PCL530-3; (●) PCL1250-2; (▲) PCL2000-2; (□) PDEA500-2; (○) PDEA1000-2; (△) PDEA2000-2.

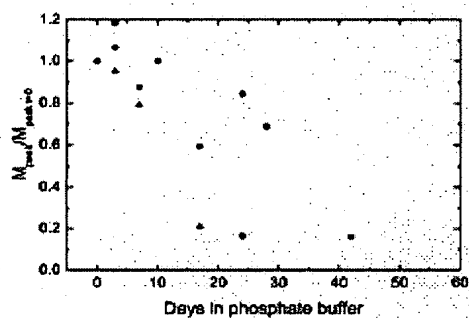


Figure 6. Molar mass as a function of hydrolysis time of different PCL-based PUURs at 77 °C: (■) PCL530-3; (●) PCL1250-2; (▲) PCL2000-2.